NEW DEVELOPMENTS IN THE MOLECULAR PHARMACOLOGY OF NPY: THE SEARCH FOR THE FEEDING RECEPTOR, D. R. Gehlert, R. A. Gadski, D. Larhammar and S. Lyengar, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN and Department of Pharmacology, Uppsala University, Uppsala, Sweden

One of the most dramatic effects of centrally administered neuropeptide Y (NPY) and peptide YY (PYY) is a rapid induction of food intake. Through combination of both feeding and metabolic responses, chronically administered NPY induces obesity in rodents including increased white adipose tissue, decreased metabolism and insulin resistance. The pharmacology of the feeding response to NPY indicates a receptor with many of the properties of the Y1 receptor, however, the fragment NPY2-36 exhibits increased potency and efficacy when compared to the native peptide. In addition, centrally administered NPY reduces body temperature while NPY2-36 does not suggesting receptor heterogeneity in the feeding and metabolic responses to NPY. To help delineate the receptor family for the PP-fold peptide, we have employed molecular cloning techniques. The first member of the receptor family to be cloned was the Y1 receptor that exhibits relatively high affinity for the analog Pro^{34}-NPY while having lower affinity for the C-terminal fragments of NPY. Initially, this receptor was cloned as an "orphan" peptide receptor and later identified as Y1. Using homology cloning techniques, we recently cloned a human receptor that has limited homology to the Y1 receptor. This receptor exhibits very high affinity for pancreatic polypeptide (K_i~20 pM) with somewhat lower affinity for PYY (K_i~300pM) and NPY (K_i~3 nM). The rat ortholog of this clone exhibits poor amino acid conservation (75% identity) when compared to the human. rPP1 also has very high affinity for PP but substantially lower affinity for NPY and PYY. The third receptor we have cloned is a receptor with a pharmacology similar to the classically defined Y2 receptor. This was accomplished using an expression cloning technique with a cDNA library derived from human brain. The functional implications of the activation of these receptors subtypes *in vivo* will be discussed.

Our efforts have resulted in the cloning of the most established members of the PP-fold peptide family of receptors. However, none of these receptors possesses the complete pharmacology observed when PP-fold peptides are administered centrally in feeding studies. Further characterization of central NPY/PYY receptor subtypes by molecular cloning and the development and use of specific receptor antagonists will be necessary to identify the molecular target for this response.